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ALTERNATIVES: JONAS MOVES ON AS CENTER MOVES IN

by Fran Pollner

There are more things in heaven and earth, Horatio, than are dreamt of in your philosophy.

—Hamlet, Act 1, Scene 5

With perseverance and scientific rigor, researchers have unlocked mysteries of the human condition and once-invisible mechanisms of disease-causing and healing processes.

Typically exempted from the rigors of scientific scrutiny, however, have been the "home remedies" and "unorthodox" approaches to healing collectively known as "alternative" or "complementary" medicine.



Wayne Jonas

Ironically, the public's demand that alternative medicine approaches be taken seriously enough to be accorded a place at NIH—has made them an accessible and funded subject for the kind of scrutiny that substantiates or disproves the value of any proffered remedy for human ailments.

That was the objective of Wayne Jonas and the concept that shaped his actions as director of the NIH Office of Alternative Medicine (OAM) from July 1995 until his departure at the close of 1998. Indeed, it was the premise upon which the OAM was launched by congressional mandate in 1992—that science can throw light on areas previously thought unexplored.

The first three years of OAM's existence were somewhat rocky, and the office had not really found its niche when Jonas came on board.

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NEW CLINICAL RESEARCH PLANS LEAP SPACE AND SPECIALTY BARRIERS

by Celia Hooper

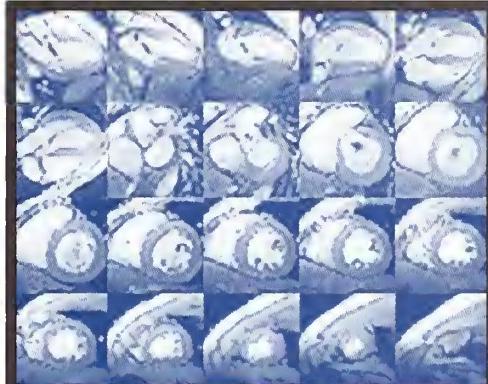
While architects and bulldozers are scratching out the physical groundwork for the new Clinical Research Center (CRC), others are at work on the programmatic groundwork, hatching plans they hope will fill the place with exciting, state-of-the-art clinical research.

With space as tight and precious as ever, proposed schemes for optimizing use of the new CRC combine creative leveraging of extant resources with selective, targeted additions of new money and positions. Three such initiatives, all at different stages of implementation, are the first waves of program changes

for Clinical Center Director John Gallin. They include establishing "Centers of Excellence" in particular areas of clinical research, fostering collaborations between clinical and laboratory scientists, and establishing new partnerships with local hospitals and medical centers.

Background

In an address to a joint meeting of the scientific and clinical directors on November 4 last year, Gallin made it clear that it's not just the lure of an attractive new building that's spurring plans to bring top-flight clinical research to the Clinical Center. It's also the old bugbears of declining patient enrollment, appro-



Andrew Arai, Fred Epstein, and Bob Balaban

Montage of a whole heart with a valve error, as captured by magnetic resonance imaging—an instrumental piece of the collaboration between NHLBI and nearby Suburban Hospital

priate resource planning, and clinical researchers' morale—is issues sketched out in the Straus report in 1997 (see *The NIH Catalyst*, May-June 1997, page 1).

Marching orders for NIH must be to increase patient census while sustaining top-quality science and improving planning, Gallin said. This is no easy task because the patient

population at any given time is based on the prior projections from each of more than a dozen institutes and divisions—their best estimates of numbers of protocols and patients to be recruited.

These estimates are translated into demand for Clinical Center resources, forming the basis

Clinical Center Earns Certification As Transplant Center To Support New Translational Research Programs

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COLLABORATIVE MANAGEMENT OF CHANGE WILL LEAD CLINICAL CENTER INTO THE FUTURE



John Gallin

After almost 5 years as Clinical Center director, I am constantly reminded that many of the issues facing this organization are similar to those facing academic centers and other hospitals across the country.

Sometimes seemingly beset on all sides, we face common problems in recruiting patients, providing equitable access to services, and controlling costs while maintaining high-quality patient care and services and incorporating new technologies. The specific answers are not simple, nor are they the same for all health-care institutions; however, a general approach shared by all hospitals is the need to embrace change and manage it effectively—distinguishing threats from opportunities and balancing tradition and innovation.

At the Clinical Center, the key to managing change over the past few years has been collaboration in planning and governance.

Many positive changes are underway at the Clinical Center, the most visible being construction of the new Mark O. Hatfield Clinical Research Center (CRC). Others include evolution of a new governance structure, implementation of a new "school tax" funding approach, and planning for new technologies to facilitate protocol mapping, cost accounting, and imaging. At the same time, the Clinical Center has staved off some threatening changes, such as privatization and third-party payments.

Whether implementing positive changes or fighting off threats, we have learned that thoughtful planning, zealous communication, and increased collaboration among institutes, patients, and staff are essential.

In fact, success is driven by effective collaboration in patient care, science, management, and finance.

Our collective task must now be to foster a robust clinical research program, and three key assignments in meeting this challenge are 1) attracting and retaining clinical investigators, 2) recruiting patients, and 3) achieving operational efficiencies. Within the NIH intramural clinical research program, new collaborative teams, councils, and advisory groups representing a broad variety of interests have been established to tackle these jobs.

Attracting Clinical Investigators

In 1997 the Clinical Research Revitalization Committee, a trans-institute team chaired by Stephen Straus, NIAID, identified several improvements to help retain and recruit outstanding clinical investigators. Their recommendations included modifications in personnel and funding mechanisms, promotion and tenure processes, and research support and training. The committee also called for bench-to-bedside research proposals to promote collaboration between laboratories and called for the development of "Centers of Excellence" where leading-edge science is coupled with best practices in clinical medicine (See "Clinical Research Plans," p. 1). Many of these recommendations have been implemented or are now in the works.

Meanwhile, Michael Gottesman, deputy director for intramural research, has been contemplating NIH's Final Frontier—space. He has been invited to the next Clinical Center Board of Governors meeting to discuss how space limitations affect recruitment of clinical investigators and, consequently, patient activity.

There is hope: After completion of the new CRC, a suggested phased north- and south-side renovation of Building 10 E and F could allow for some expansion of space for new clinical investigators.

Recruiting Patients

The Medical Executive Committee (MEC) chaired by Scott Whitcup, clinical director of NEI, made several important decisions this year that should improve patient recruitment. For example, when the MEC learned that an increasing number of individuals now refer themselves to medical protocols

via the web, the panel revised NIH's physician referral policy to allow some flexibility in patient referrals that flow in via this route.

Additionally, a Clinical Center contract designed to improve patient recruitment and raise awareness of NIH intramural programs was awarded in 1998. Assessing how the Clinical Center is viewed by the world and how best to communicate its vision are key features of this initiative. The Institutes and Centers have been providing input for this project and, beginning in 1999, the Clinical Center will survey patients to identify ways to improve service and recruitment. These patient-oriented initiatives are

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facilitated by valued input from the Patient Advisory Group, a new standing committee of former and current patients.

Achieving Operational Efficiencies

The Clinical Center Board of Governors, first convened in October 1996, is our prime model of effective collaborative governance. The Board, comprised of institute leaders and outside experts in health-care management, has been particularly helpful on budgetary issues and operational improvements. At a time when Clinical Center costs were becoming more unpredictable for the institutes amidst declining patient rolls, the Board suggested the new "school tax" funding model to stabilize the CC budget and boost patient numbers while providing fiscal predictability for the institutes. This new funding model will be implemented in fiscal year 2000.

Two other programs were instituted in 1998 to improve operational efficiency and generate cost savings: operational reviews for Clinical Center departments and a cost-savings incentives program. The reviews, conducted by outside experts, are designed to offer Clinical Center managers insight, advice, and assessment. Two departments reviewed in 1998 received constructive recommendations that will promote effective customer-responsive management, better service, improved quality, and cost reductions. The cost-savings incentives program, designed to reward cost-savings efforts by Clinical Center employees, was instituted by Clinical Center departments under the leadership of Adrienne Farrar, chief of social work.

The Clinical Center Advisory Council (CCAC), established in 1997, facilitates collaboration with the institutes and ensures that they have a strong voice in Clinical Center issues that affect their intramural clinical research programs. Membership consists of representation from the five largest institutes using Clinical Center services and, on a rotating basis, three smaller user institutes.

The CCAC has provided input on many aspects of the budget process, including a definition for new institute initiatives and how they should be funded under the "school tax" model. This group has also managed the use

of carryover funds and provided strong guidance on operational issues surrounding the institutes' clinical research programs. But the CCAC's best demonstration of its consensus-building prowess came in its planning for the utilization of the new CRC. The formation of Partners Groups last year by the Council created a structure of teams to provide direction throughout the Design Development phase of construction. As we continue to prepare for the new CRC, we will establish new collaborative governing structures for shared patient-care units.

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THIS NEW FUNDING MODEL
WILL BE IMPLEMENTED IN FISCAL
YEAR 2000.

1999 and Beyond

A major effort in 1999 will be planning for a Clinical Research Information System (CRIS), a new system to replace the current Medical Information System. Much more than just a static information system, CRIS will help the CC support operational efficiencies and other administrative initiatives by transferring data to support activity-based costing, protocol mapping, and performance measurement. CRIS will also contribute in many new ways to the support and advancement of clinical research, for example, through its inclusion of powerful medical informatics and imaging tools that allow viewing of digital images from any terminal in the hospital.

Collaboration is not new to NIH—but its increasing presence in managing

the Clinical Center has helped to foster unity and valuable strategies essential to making needed changes. Such adaptation is central to success—in science and management. As we begin a new year, I welcome input from everyone on how we can make the Clinical Center a better place to work, to practice medicine, to support clinical research, and to care for patients. Send your e-mail suggestions to: <jgallin@nih.gov>.

—John I. Gallin
Director, Clinical Center

CATALYTIC REACTIONS

On Slides and CVs

The blurb on "slide preparation" attributed to me on page 3 of the last issue (November-December 1998) is a substantial distortion of my e-mail "letter to the editor."

As you can see [in the "subject" of the e-mail—*Ed.*], my comment was in reference to the preparation of CVs, not slides (in reference not to the slide preparation article in *The NIH Catalyst*, May-June 1998, but to the CV preparation article in the September-October 1998 issue). A slide in html makes no sense! On the other hand, a brief, attractive CV on a postdoc's web page might get her a job interview.

A correction would be much appreciated.

In case that you would like my view on "slide preparation," I would say: 1) make them large, that is, readable from as far away as necessary; 2) keep them sparse—your talk should be complementary to the slide's contents, and busy slides can confuse rather than inform; 3) avoid fancy coloring, since it is often distracting or worse, invisible. (Have you seen a red curve or text in the Masur Auditorium recently?)

Thank you. Regards again.

—Ray Mejia, NHLBI and NIDDK

—Sorry, Ray, when you wrote that "it is wise to prepare one in html, and make it available to appropriate services and/or requests and via a personal web page," we inexplicably decided the "one" referred to slides—didn't even think of CVs (maybe because we're so (unjustifiably) secure in our jobs. . . .

DIVERSITY ISSUES LEAP OFF THE PAGE ONTO THE CAMPUS

Ron King, chief of the NHGRI technology transfer office, stood at the mike and scanned the faces of those occupying the seats around him in Wilson Hall, where a public forum on "diversity in the workplace" had just opened up for audience questions and comments.

"I don't see too many rank-and-file scientists here," he said, registering his disappointment before commenting on the issues raised.

During the preceding hour, there had been a reading from a novel that dramatized race, sex, and class dynamics in a Los Angeles bank, followed by a panel discussion applying the book's issues to the scientific world at NIH. The forum, held November 30, was the second of a scheduled five in the Diversity Book Bridge Project offered by the NIH Office of Equal Opportunity. According to Gary Morin, an OEO program analyst for diversity, this particular forum was "aimed at scientists in the workplace, while the series overall is aimed at all NIH employees—scientists or administrators, rank-and-file or management."

Leaders and Readers

Offsetting the absence of the "rank and file," however, King observed, was the presence of some NIH policymakers. "Top-down leadership is important, and I'm glad they're here," he said, referring to NIH Deputy Director Ruth Kirschstein and Michael Gottesman, deputy director for intramural research, "because they set the tone, and they communicate."

That thought was echoed after the forum by OEO director Naomi Churchill-Earp: "It's hard to get the scientists out of their labs—and we've tried—but Michael [Gottesman] will take the word to the scientific directors, and the scientific directors will take it to the labs."

Gottesman had opened the session with some words of his own. His academic credentials, he said, had not prepared him for the challenges represented in striving for diversity in the scientific workforce. "I read the book from cover to cover," he said of Bebe Moore Campbell's *Brothers and Sisters*, the "text" that serves as the jumping-off point for the diversity discussions, "and it has been eye opening in many respects."

"I feel an enormous responsibility to do whatever can be done at NIH to improve communication" among people

of different backgrounds, he said. He cited the incipient NIH Academy, designed to draw students from all walks of society and at different points in their academic lives, as a project that will contribute to diversifying both NIH and the overarching biomedical research community. Based on the recommendations of the Slavkin Report (the report of the Committee for the Recruitment of Ethnically Diverse Young Talent into Biomedical Research, chaired by NIDCR Director Harold Slavkin), the academy will provide a "warm, nurturing environment for students at all levels to come to learn about research," Gottesman said. [The March-April 1999 issue of *The NIH Catalyst* will explore the Slavkin Report, the NIH Academy, and related matters.]

Reading dialogue from Chapter 25 of the novel, ad hoc NIH actors brought to life the characters at Angel City National Bank and the issues they confronted: The bank's loan department was almost all white, and so were the bank's loan recipients; the lenders were more likely to bend the requirements for a loan when the prospective recipient was a promising white person who needed a little guidance and with whom the lender felt comfortable; people who objected to calls for a minority loan program were strangely blind to the fact that the current system was nothing more or less than "affirmative action for white people."

In the ensuing panel discussion, participants drew parallels between the Angel City loan department and the NIH tenure apparatus. J. Ricardo Martinez, a former member of the NIDR (now NIDCR) advisory council subcommittee on minority affairs and newly recruited NIDCR extramural director, remarked on the continuing paucity of minority participation in NIH programs: "It's 10 years later and I'm back, and I must say that the panorama has improved a little but not much. The discrepancy between the percent of minorities in the population and the percent of minorities in the scientific community is unchanged."



Ron King



Fran Pollner
Joan P. Schwartz

Stats

The numbers presented by Joan Schwartz, NINDS section chief and assistant director of the Office of Intramural Research, painted a similarly grim picture regarding the awarding of tenure to women and underrepresented minorities.

Despite recognition earlier in the decade of the need to recruit, promote, and tenure fair numbers of women and minorities and thus to carefully select members of every search committee and to revamp tenure procedures, the measures taken to remedy systemic inequities break down at the point of tenure-track selection.



Fran Pollner
Actors: (left to right) NIHers Ludlow McKay, Karen O'Steen, Linda Morris, and John Medina bring words to life

Statistics related to recruitment and promotion, though not sterling, are at least in the right direction: from 1992 to 1996, the percentage of women among NIH scientific directors rose from 0 to 14 percent, of lab and branch chiefs from 4 to 10 percent, and of section chiefs

from 13 to 18 percent. But the number of women in tenure track from the end of 1995 to the end of 1997 actually decreased from 29.9 to 25.3 percent; and though the percent of minorities recruited to tenure track increased slightly from nearly 20.7 to 22.9 percent, the percent of underrepresented minorities decreased from 8.3 to 6.3 (about 4 percent Hispanics and 2 percent African-Americans). "Just having a representative on a committee is not enough," Schwartz observed.

"We need to revisit diversity in the NIH workforce," Martinez commented. "Perhaps the scientific workforce here and outside is becoming more diverse at the expense of native-born black Americans and others. The NIH Academy," he added, "is a very interesting concept that should be moved into the extramural community as well."

He addressed the "irony" of the appeal to Congress by this country's biotech companies that visa restrictions for technically trained foreigners be loos-

by Fran Pollner

ened because they can't find trained people in this country. "That's a bad reflection on us, and I'm not being xenophobic," Martinez said.

Several speakers pointed to the role of education, from the earliest through the postgraduate years, as a critical element in diversifying the scientific community. But NHGRI's King cautioned against "putting all our energy into filling the pipeline. If there's a plug at the other end, filling it won't do much good. Where are all these people going? Where will these young minds coming into the [NIH] Academy go? We need to follow them and [have answers] when we're asked."

Kerri Burton-Danner, an associate ombudsman at the NIH Center for Cooperative Resolution (also known as the Ombudsman Office), wove together some of the themes of the novel *Brothers and Sisters* and the forum discussion in observing that in resolving disputes at NIH, "sometimes whites don't know how much privilege their skin confers." She cited herself as an example of the need for and wisdom of science programs pointed toward underrepresented minorities. She benefited, she said, from NIH-sponsored programs throughout her scientific training, including a high school summer science program and the MARC (Minority Access to Research Careers) honors program while attending Clark Atlanta University, an HBCU (historically black college or university), before completing her doctoral work in behavioral neuroscience at the University of Alabama at Birmingham. Referring to earlier remarks about diversity at NIH, she pointed out that even with attempts to fill the pipeline, in many cases, native-born minority students and fellows do not feel readily accepted into mainstream scientific culture—an observation that brought murmurs of agreement from the panelists.

Out of time, the discussion ended shortly after. As Wilson Hall emptied, program moderator Mary Brown ob-



Afterwords: Seminar organizer Mary Brown (left) talks with panelist George Counts, of NIAID, and NIH's first ombudsman, Dave Robinson



Kerri Burton-Danner

served that "the dialogue could certainly have lasted longer, but I think there will be follow-up." Brown, a professor of American and African-American literature at Prince George's (Maryland) Community College, is the coordinator of the Diversity Book Bridge Project, a program she began at her own institution in the fall of 1997 and was contracted by NIH's OEO to replicate here. ■

Two More Bridges

Two forums remain in the series: Community Involvement, March 29; and Bebe Moore Campbell Visits NIH, May 24. Both will be held in Building 1, 3rd floor, Wilson Hall, and begin at 9 a.m. *Brothers and Sisters* is available through the R & W. For more information, call 496-4628. ■

Diversity Council Readies Two Reports

The NIH Diversity Council has established a Task Force on Diversity in Recruitment at NIH to review current practices and advise how best to maintain diversity in recruitment and retention. The task force has been conducting focus groups around campus; its report and recommendations are under review and due out this spring.

The Council's Disability Awareness Task Force has also completed its report, to be released this spring, on reasonable accommodations at NIH and its leased facilities and the accessibility of NIH-provided transportation services.

Persons of varied ages, races, sexes, and sexual orientation make up the Diversity Council, which includes representatives of the intramural and extramural communities; the scientific, administrative, and wage-grade staff; and the commissioned corps.

For more information, contact Carolyn Hunter in the Office of Equal Opportunity at 402-3663. ■

CALLING ALL LABS: CLIA HELP ON CAMPUS

Many of NIH's research laboratories are also "clinical laboratories" according to the definitions encompassed in the Clinical Laboratory Improvement Amendments of 1988 (CLIA 88) and must be certified as meeting CLIA operational standards.

The Clinical Center Clinical Pathology Department has established a centralized CLIA Resource Center to help institute laboratories meet these standards.

CLIA 88 covers all laboratory tests performed on "materials derived from the human body" for the diagnosis, prevention, treatment, or monitoring of patients, as well as the assessment of patient health or impairment. Any NIH laboratory that performs tests on human specimens that have a patient-linked unique identifier and that generates information used in the management of the patient's condition or results that are reported to the patient or a physician must conform with CLIA 88. CLIA 88 is the legal foundation of the federal government's regulatory oversight of laboratory testing performed in the United States.

Neither test volume nor the presence or absence of charges affects a laboratory's status—only the nature of the tests performed. The law requires that the laboratory define the level of complexity of its testing within broad categories, and most testing at NIH falls into the "highly complex" classification. Somewhat less tightly regulated—but regulated nonetheless—are tests generally performed in clinics, including those at NIH, that fall under the "moderately complex" category of Physician Performed Microscopy Procedures.

Labs that perform highly and moderately complex tests are subject to standards in proficiency testing, patient test management, quality control, quality assurance, and personnel qualifications.

CLIA certification is for two years and contingent on inspection. Labs must fill out a CLIA registration form and prepare for inspection by a CLIA inspector (from the Health Care Financing Administration). The usual fee is \$400.

The CLIA Resource Center will assist lab directors and staff in filing their registration forms and preparing for inspection. For information about CLIA 88 and the NIH CLIA Resource Center, contact Peggy Spina at <pspina@cc.nih.gov> or Thomas Fleisher at <tfleisher@nih.gov>. The Clinical pathology Department may be reached at 496-5668 (phone) and 402-1612 (fax). ■

CLINICAL RESEARCH SCHEMAS

continued from page 1

for hiring Clinical Center support staff and making quantity purchases of supplies. In the face of such uncertainties as marketplace forces and political winds, institutes have tended to overestimate clinical research needs—as they did, by 17 percent, last year—rather than underestimate and risk insufficient support of an approved protocol.

Reversing the downward trend in patient enrollment would be easier to accomplish if it weren't for limitations on lab and office space—just hire more clinical investigators and get them rolling on some new research protocols. When the new CRC is completed in 2002, there *will* be some net additional space. Researchers from the old corridors of Building 10 will be relocated to the new building, allowing for some decompression and new recruitment. Space allocations in the new CRC will rest on careful selection criteria, including the merits of the research, the need for proximity to patients, and the need for proximity to other clinical research programs in the CRC. Ultimately, creaky infrastructure will be decommissioned and closed.

Imaging Alliance

Of the proposed solutions for expanding the use of the Clinical Center, farthest along toward implementation is a project that emerged indirectly from discussions 18 months ago with administrators at Johns Hopkins University's medical school in Baltimore. In Hopkins' pursuit of a partnership with Suburban Hospital—which is just across Old Georgetown Road from NIH—the university leaders let both Suburban and NIH know that they would be much more interested in the relationship with Suburban if the hospital, in turn, had a close relationship with NIH. The Hopkins executives subsequently left the university for jobs elsewhere, but the idea of a partnership between Hopkins, Suburban, and NIH stuck. The most conspicuous areas for cooperation are with Suburban, says Gallin, particularly in hospital services NIH lacks, such as the emergency room.

Meanwhile, NHLBI investigators Bob Balaban and Andrew Arai had been developing multimodal cardiovascular im-

aging instruments and techniques and using them to image chronic heart disease patients in the Clinical Center. Recognizing an opportunity to apply the techniques to Suburban's emergency room patients with acute myocardial infarction, Balaban became the project officer for what blossomed into a three-way partnership between Suburban's emergency room, NHLBI, and NINDS.

To study patients with heart attacks, the heart institute has bought a powerful magnetic resonance imaging (MRI) instrument designed by Balaban's lab and General Electric for one-stop, multimodality imaging of the beating heart with excellent 1-mm resolution. The instrument will be installed at Suburban and, without having to move pa-



Measurement of cardiac contraction using a grid-tagging method

Andrew Arai, Fred Epstein, and Bob Balaban

tients to a series of imaging instruments, doctors there will be able to conduct one 45-minute scan to view the anatomy of the heart, its perfusion—how much blood is getting to each part—how well each section of the myocardium is beating, and the viability, scarring, and salvageability of all parts of the heart. Balaban says the imaging will allow doctors “to do a much better job in making decisions in triaging patients with acute chest pain”—for example, whether to catheterize a patient, send him or her home, or give thrombolytic therapy.

While Suburban's patients will receive state-of-the-art imaging, Balaban's lab will have research access, for the first time, to patients with acute heart disease. The new instrument, which should be up and running by the end of April, will give Suburban instant cachet as one of fewer than a dozen medical facilities in the country with the latest in heart-imaging technology.

Balaban is elated about the partnership and says his colleagues at Suburban feel the same way. “They are very excited. This is their first major collaboration with NIH. So far it looks like a win-win situation for both sides of Old

Georgetown Road.” Balaban adds that he thinks the program would serve well as a model for partnerships with other hospitals and academic centers in the area. “Through these arrangements, NIH could expand its influence on medicine in the area,” Balaban observes. “In the past, our research hasn't had nearly the impact it should on the quality of medical care here. This is a step forward.”

NINDS is taking a slightly different approach in its collaboration with Suburban Hospital. Rather than buying an entire MRI instrument based on Balaban's fast-scanning techniques, they will buy a 20% share of a head-imaging instrument based on the innovative technology. NINDS will then launch a protocol at Suburban to study stroke treat-

ment, starting with an expected 200 stroke patients per year—again, one of the first intramural protocols to focus on emergency room patients. Balaban anticipates that some NIH time on the both the heart- and head-imaging instruments will be made available to institutes other than NHLBI and NINDS and scheduling

of such use of the machines will be handled by the In-Vivo NMR Center steering committee.

Bench-to-Bedside Partnerships

Just emerging from the concept stage is a proposal (among the recommendations in the Straus committee report) to pair basic and clinical or translational scientists on research projects that draw from each partner's strength. In December, Deputy Director for Intramural Research Michael Gottesman issued a call for statements of interest in such a program, which would provide up to three years of support for bench-to-bedside collaborations. Investigators could come from any institute or pair of institutes, and must include the active involvement of both a lab-based and a clinic-based investigator, with sign-offs on the work coming from at least one scientific director and one clinical director. “Much to our delight,” Gallin reports, “we had a tremendous response” within a few weeks of the call, and 44 submissions were reviewed. Gallin and Gottesman winnowed these to 10 and will request formal proposals for support of up to \$100,000 per year from an NIH-wide pot—possibly money saved by cost-cut-

ting measures at the Clinical Center.

Stephen Straus, chief of the Laboratory of Clinical Investigation in NIAID, has been conducting clinical research in collaboration with scientists throughout NIH for 20 years and points out that the practice of pairing clinical and basic researchers from different institutes has been going on for years. But he has high hopes that the new program and infusion of money "will bring together lab and clinical investigators in a new way. This program makes a positive statement that NIH will encourage this kind of work," Straus says. Both he and Gallin expect that the institutes will offer support to good bench-to-bedside proposals that are not selected for central funding.

Centers of Excellence

Still in planning stages, the proposal for "Centers of Excellence" in clinical research is conceptually the most dramatic change for NIH. The inspiration for such centers comes from regional medical facilities, which are increasingly attempting to corner markets in certain medical specialties. This approach broadens the geographic area from which the hospitals draw patients and income. Gallin observes that the managed care industry questions why they would refer patients to NIH "rather than Mass General, [Johns] Hopkins, or a local institution. We have to have something special to offer and can with our centers."

NIH's centers, as described by NIDDK's Jake Liang and Straus in a recent proposal, would draw on traditional areas of NIH research strength—autoimmune diseases, behavioral medicine, or hepatitis, for example—and perhaps build upon the models established by current interinstitute training programs in genetics and endocrinology. Gallin envisions providing some central space and staff for the centers and recruiting or designating current NIH staff who are leaders in the fields to run the programs, which would stand at the center of a swarm of basic, translational, and clinical research, training, and shared lectures and rounds. Efforts are underway to identify the best potential research areas to cultivate as Centers of Excellence.

Gallin views the Centers of Excellence as the most exciting of the innovations at hand. "Once we have these centers, I could see some serious use of them to advertise nationally what we do at the Clinical Center," he says. Increased visibility would likely result in the spillover

of new referrals and congressional interest to all of the intramural clinical research programs, he predicts.

Other Advances

Beyond these three proposals, Gallin sees other programmatic improvements in the works. The year 1999 will witness the launch of a major new emphasis on pain and palliative care at the Clinical Center, for example. After a campus-wide summit conference in November, NINDS, NIDCR, and the Clinical Center are working in concert both to improve management of pain for patients and to support pain research by the institutes. The main recommendation to emanate from the summit, Gallin says, was that a "comprehensive service in pain and palliative care" be

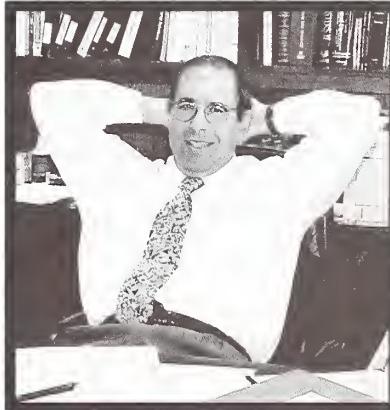
organized. He expects to recruit physicians and nurse practitioners for the service this spring and to launch it by this summer. Ultimately, the team will include expertise in psychiatry, neurology, pharmacology, oncology, social work, and ethics, as well as pain assessment and management and the handling of chemotherapy complications.

One small experiment underway is in the Clinical Center's hiring of a part-time consultant in internal medicine. In the past, the individual institutes have largely been responsible for identifying outside specialty consultants to assist with ancillary medical problems arising for protocol patients. Institutes frequently draw on one another's expertise to handle these problems, as when NCI, for example, turns to NIMH practitioners for help with psychiatric issues arising in the treatment of a cancer patient. Gallin says that the Medical Executive Committee requested that he identify an internist who could provide consultation to several institutes that did not have access to that expertise. His selection was Fred Gill, a seasoned Bethesda physician who was on staff at NIAID before going into private practice. Gallin says he'll review the results of the experiment in six months and see how well Gill's consultations have satisfied institute "customers."

The most expensive change underway at the Clinical Center at the moment involves infrastructure rather than programs, Gallin says. That would be the new Clinical Research Information System, or CRIS. Costing about \$30 million, CRIS will provide a comprehensive, integrated administrative and research information system—with all the bells and whistles. In addition to supporting a new and desperately needed activity-based cost-accounting system, which will help improve planning and finances, the system will permit the storage and delivery of all types of images, including anatomic, radiologic, and those derived from tests and functional and structural imaging of everything from the retina to the colon. CRIS will seamlessly link scheduling, protocol mapping, and connections between labs responsible for patient tests and specimen analysis. The project is expected to take three years, Gallin says.

So Far, So Good

Will the plans and changes spark the spiritual renaissance so fervently sought by clinical leaders at NIH? Straus says he, like others, is taking a wait-and-see stance, but he does detect change in the air. "The sense I have is that there is a cautious optimism at this point. The dialogue from NIH is very encouraging now, but clinical investigators are waiting to see changes actually taking place," Straus says. The most positive signs he sees already are in recruitment. "For the first time in a long time, there are a large number of recruitments for investigators to do real patient-oriented research. There was little or none of that before. I am encouraged." The best news, Straus says from his view on some of the search committees, is that "We are getting good applicants. This has always been a phenomenal place to come to do research. Now they are coming not just for the research resources but for the new building—it's the physical evidence of the new NIH commitment to patient-oriented research and that is appealing to new applicants."



John Gallin

Fran Pollner

NIH TAKES ON TRANSPLANTATION AS PART OF NIDDK-NAVY PROGRAM TO TACKLE TYPE 1 DIABETES AND OTHER AUTOIMMUNE DISEASES

The NIH Clinical Center will exit the 20th century as an active organ- and tissue-transplant center, with several dozen novel kidney and pancreatic islet transplants expected to be carried out there between May and year's end.

The operations will take place in an NIDDK abuzz with intellectual excitement over immune-modulating therapies that may eliminate the need for immunosuppressive drugs to prevent graft rejection. A renovated Ward 11 East in Building 10 is becoming a dedicated transplant site, a nexus for the translational research that will find its way from the laboratory of a new NIDDK research branch into clinical studies.

Opportunity knocked three times at once to inspire the creation of such a program, according to NIDDK scientific director Allen Spiegel: an overarching renewal of appreciation for clinical research in general and for the need to expand research on the pathogenesis and treatment of type 1 diabetes in particular; results compelling enough in animals to warrant clinical studies of a new approach to kidney and islet cell transplantation; and coincidental plans to reorganize both the NIH Clinical Center and the military medical research establishment that eased the way to a collaborative effort.

The new Transplantation and Autoimmunity Research Branch is a joint NIDDK-Navy venture. It was initiated by Spiegel, who enlisted the Navy personnel and orchestrated the project that would entail securing UNOS (United Network for Organ Sharing) certification and NIDDK collaboration with an array of entities both outside and within NIH.

In the former category are the Navy, the Army, the University of Wisconsin, the University of Miami, and the industry partners of the Navy researchers. In the latter are the Clinical Center, NCI and NHLBI bone marrow transplant researchers, and the NIH stem-cell-processing apparatus. Moreover, if early clinical (phase 1 and 2) trials here on campus produce the kinds of results that all involved parties are betting on, NIAID's

newly formed Collaborative Network for Clinical Research on Immune Tolerance may well be pressed into action to conduct multicenter, phase 3 clinical trials.

The program will "have ripple effects at NIH that go well beyond NIDDK," says Spiegel, whose excitement over the project is tempered only by concern that his own role not be overemphasized. "I fostered this initiative," he says, "but it's not my science. The science belongs to the principal investigators"—Dave Harlan and Allan

Kirk, Navy researchers whose studies of reagents to block the costimulatory pathway in the immune response have resulted in the acceptance without immune suppression of mismatched kidney and pancreatic allografts in rhesus monkeys. "Everything they do—kidney and islet cell transplantation and research into the pathogenesis of type 1 diabetes—could not be more programmatically relevant to what we do," Spiegel notes.

UNOS certification, he adds, was spearheaded by Dave Henderson, CC deputy director for clinical care, who, together with NIDDK chief administrator Barbara Merchant, mobilized the Clinical Center to secure needed space, equipment, and staff. Henderson, in turn, points to the commitment of the CC staff and the "uncompromising support" of CC Director John Gallin as the forces behind the rapid changes. And PIs

Harlan and Kirk marvel at the "model of cooperation" exhibited by the civilian and military parties in organizing the project—"all crossing boundaries to achieve the same goals, all driven by enthusiasm for the promise of the sci-

ence," says Kirk.

That enthusiasm greeted Harlan, Kirk, and Spiegel throughout 1998, as they delivered multiple presentations on the science, logistics, and promise of the bench-to-bedside initiative. They spoke before the Clinical Center Advisory Council, the Medical Board, a Clinical Center town meeting, bench-to-bedside grand rounds, and gatherings of institute and scientific directors. At no point was the science questioned or approval withheld. Rather, there was activity in all quarters to make things happen.

The new Transplantation and Autoimmunity Research Branch will be housed physically across Rockville Pike at the National Naval Medical Center's Armed Forces Radiobiology Research Institute (AFRRI)—4,000 square feet of laboratory and office space and an adjoining veterinary facility that is being renovated at NIDDK expense and should be available by late fall. "Their retrenchment is an opportunity for us," Spiegel remarks of the military's string of base closures that includes shutting down the Naval Medical Research Institute and the consolidation of Army and Navy research laboratories at a joint site in Silver Spring, Maryland.

The preclinical work—in the laboratory and with small and large animals—will unfold at the AFRRI site and then move into the Clinical Center, along with Harlan and Kirk, for testing in humans. "Bench and clinical research go hand-in-hand," Harlan notes, "and we go with it."

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—Allan Kirk

plant section while maintaining his Navy status. "Both the Navy and the Public Health Service recognize that it's a more logical fit for me to be with the PHS," says Harlan, who heads the Navy's immune cell biology program and whose



Fran Pollner

by Fran Pollner

research and intense interest in type 1 diabetes gained him a seat several years ago as the Department of Defense liaison on the NIDDK Advisory Council.

His primary objective as an endocrinologist, he says, is to "see a new treatment and potential cure" for type 1 diabetes. While transplantation is clearly a focus of the new branch—and the team expects to perform between 50 and 100 kidney and islet cell transplants a year—"don't forget that this is a transplantation *and autoimmunity* branch; we anticipate protocols down the road involving type 1 diabetes markers—and other autoimmune diseases will come along," Harlan says.

Moreover, even protocols involving transplant patients may not necessarily entail transplantation. Subsets of pre- and posttransplant patients present unique and challenging problems, Kirk observes. On the one hand are patients who appear immunologically unfit for transplant and on the other are those vulnerable

to chronic rejection after successful transplant. There will be protocols in these areas as well as protocols to introduce novel immune-modulating approaches to kidney and islet cell transplant procedures.

"There are many reasons a transplant center at NIH makes sense," says Kirk, a transplantation surgeon with a commitment to research. "There are a number of therapies we're working on that look promising for revolutionizing the way transplantation is done, and there are a lot of very good basic investigators in transplant immunology at NIH right now who have no place to go when they want to transition their bench research into the clinic."

Current methods to prevent rejection, he notes, work well against T-cell-mediated rejection but not against antibody-mediated rejection, the problem of about 30 percent of patients on the kidney transplant waiting list. But since this "presensitized" population amounts to no greater than perhaps 10,000 pa-

tients, it does not inspire commercial interest. Similarly, the extramural community does not fund "proof-of-concept fishing expeditions" to identify reagents that modulate antibody response. But NIH, Kirk observes, has always been the ideal venue for research that industry and academia cannot easily accommodate. "We're not trying to be a large, aggressive, commercial enterprise, but to take specific identified problems and transition bench research into the clinic for the first time. And when we find things that look promising, we want to deliver them to the extramural community in an expedient fashion so they can be assayed in large multicentered trials," he says, referring to the NIAID network.

The Science

Costimulatory blockade, the anti-rejection strategy used by Harlan and Kirk, is believed to support long-term graft function through mechanisms other than immune suppression. As the researchers explain it, immune mechanisms are triggered when a specific antigen-

presenting cell meets a T-cell receptor on the host T-cell. The costimulatory event, nonspecific but necessary to trigger the immune response, involves one protein on the antigen-presenting cell and one protein on the T-cell. If the first meeting occurs but the costimulatory pathway is blocked, that is "not a neutral event," Spiegel notes. Rather, says Harlan, the "immune response against that specific antigen does not occur, and this immune system inactivity appears to be quite stable." Costimulatory blockade, then, blocks graft rejection not by inducing global immune suppression, as current drugs do, but by creating what the investigators call "immune re-education." Clinical testing of monoclonal antibodies against these costimulatory factors is necessarily complex: target, timing, dose, and duration must all be determined.

The rationale behind costimulatory blockade, Kirk notes, "is to use the physiologic mechanisms of immune modulation to teach the immune system that

the organ that has been transplanted is a benign functional organ that should not be removed. Conventional immune suppression "doesn't take advantage of our immune system's ability to learn" Kirk notes, "but some fairly fundamental advances in the field in the last 10 years have revealed how the system teaches itself what to respond and not respond to." Harlan points to current and former NIH investigators who have been "leading the way—Ron Schwartz, Mark Jenkins, Al Singer, Richard Hodes, Polly Matzinger, Helen Quill"

Based on *in vitro* and mouse studies of other investigators, Harlan and Kirk pioneered costimulatory blockade in nonhuman primates, testing the ability of anti-CD40 ligand to protect against rejection of mismatched kidney allografts in rhesus monkeys. Not only are the animals surviving and maintaining their new organs, they are doing so without any immunosuppressive therapy. Moreover, there have been no signs of infection, complications, or side effects. Such results, Spiegel says, are "compelling," even though the numbers are small. The team had similar success in the islet cell transplant arena in studies done in collaboration with Norma Kenyon and Camillo Ricordi, colleagues at the University of Miami Diabetes Research Institute, who demonstrated that costimulatory blockade after transplanting insulin-producing islets from mismatched donor monkeys into pancreatectomized monkeys consistently lead to insulin independence.

Harlan and Kirk began their collaboration several years ago, when Kirk was about to begin a transplantation fellowship under Stuart Knechtle at the University of Wisconsin. Harlan had been doing research on the costimulatory pathway and had been looking for a "gifted academic surgeon when, as an answer beyond my wildest dreams, Dr. Kirk knocked on the door. He was about to start his fellowship, had a four-year Navy obligation, and was looking for a way to work with us—to do both transplantation clinically and be involved in a research program," Harlan recounts.

In concert with commercial CRADA partners, the Navy-Wisconsin team tested several reagents that appeared to have efficacy in preventing rejection of transplanted organs, including various forms of anti-CD40 ligand (renamed anti-CD154) and anti-B7.



Dave Harlan (left) and Allan Kirk

Thus far, the longest kidney graft survival in the rhesus monkeys—with no signs of toxicity and no need for immune suppression—is approaching two years; the longest followup for pancreatic islet cells is now one year.

The investigators are well aware, however, of the differences between these healthy test animals whose organs have been removed immediately prior to the transplant procedure and humans with conditions that have destroyed their kidneys or islet cells. "There are arguments for and against the idea that the reagents we've been testing will thwart an immune system already activated against the insulin-producing pancreatic β cells, the mechanism underlying type 1 diabetes," Harlan notes, "but everyone agrees it must be tested in humans. There is no primate model for type 1 diabetes."

In creating clinical protocols for costimulatory blockade, there will be one complexity in the kidney transplant setting different from the usual approach to testing new anti-rejection therapies. Typically, a new therapy is offered in addition to conventional immunotherapy to assess whether it improves on the standard treatment. The costimulatory blockade strategy, however, demands that conventional immunosuppression be abandoned because the initial stimulus of antigen meeting T-cell is required for the costimulatory pathway agents to work. Spiegel suggests that other agents more compatible with these mechanisms might be used in the kidney transplant setting.

Logistics

Some initial kidney transplantation procedures might be performed at the University of Wisconsin and at the Walter Reed Army Medical Center, which is a collaborator in the NIDDK-Navy initiative. Further, preliminary clinical islet transplant studies using costimulatory-pathway-based strategies will likely soon be performed at the University of Miami. For the NIH initiative, Walter Reed is providing its already certified tissue-typing laboratory, which was a prerequisite for UNOS certification, as well as

two expert transplant surgeons who, with Kirk, will round out the surgical team initially. The Clinical Center is hiring new staff for inpatient nursing, OR, anesthesia, and other initiative-related positions—as is NIDDK. The OR and anesthesia staff may get their transplantation feet wet at Walter Reed and bring their expertise back to the Clinical Center. The transition, however, should be "seamless," says the CC's Henderson, who several months ago instituted weekly meetings of a "users group" that includes all CC department heads with a "stake in the program, who might need new or modified resources—pharmacy, critical care medicine, nursing, social work, rehabilitation medicine, anesthesiology, surgical services"—as well as the PIs and NIDDK, CC, and Walter Reed personnel.

There have also been discussions with NCI's Ron Gress, NHLBI's John Barrett, and the Diabetes Research Institute's Ricordi on the role of bone marrow transplant in conjunction with the new transplantation approaches to establish "microchimerism," or an increased tolerance to donor tissue through exposure to the donor's bone marrow cells. In addition, the Navy's John Chute is working with the University of Miami investigators to incorporate expanded stem cells in these studies.

Another critical piece of the project is harvesting and transplanting the pancreatic islet cells in a way that keeps them viable up to and during their delivery into the portal vein. Initially, according to Spiegel, islets for the NIDDK-Navy program will be shipped to NIH after harvest at the Miami facility—where the automated islet-isolation technique commonly used in the research setting was developed by Ricordi. But the Clinical Center's stem-cell-processing facility is "ideal technically and in every other way for islet harvesting," Spiegel notes, "so [transfusion medicine chief] Harvey Klein is sending people to Miami for training and then the harvesting will be done on site," overseen by Klein and Elizabeth Read, who runs the cell-processing fa-



Fran Pollner

11 East Before the Change: The long view (above) and up close (below)

cility. The intellectual partnership between Harlan, Kirk, and their Diabetes Research Institute collaborators will persist with regard to islet transplant studies as the protocols enter clinical trials at both centers.

Meanwhile, work has begun on 11 East to transform what had been a pediatrics unit until last December into a transplantation unit that will house eight to 10 beds and accompanying facilities. The first task, barely underway in January, was to make the bathrooms more accommodating to persons with handicaps. May 1 is the target opening date. "Everyone's pulling to make it. The Division of Engineering Services is being very creative," says Henderson. He estimates that the first year of the project will cost the Clinical Center about \$2 million—for renovation, reagents, personnel, patient care, and equipment, including an ultrasound machine and some cell-processing refinements. The outlay was endorsed by all the institute directors who will be contributing to the project's upkeep through the "school tax" mechanism.

The program's total cost was estimated at about \$5 million a year in a "news brief" that went out on the NIDDK web site late last year. That "guesstimate," Spiegel says, encompasses posttransplant outpatient costs, which any institution seeking UNOS certification is expected to be prepared to pay and which includes a "huge amount" for immunosuppressive medications.

"In the best of all possible worlds, however, there won't be any," he observes, and the costs will be much lower. ■



Dave Henderson



FIRST STEM CELL TRANSPLANTATIONS FOR CGD TAKE ROOT IN NIAID INTRAMURAL PROTOCOL

by Fran Pollner

Harry Malech is cautious but excited. "We've achieved substantial engraftment of corrected cells; if the numbers we have today remain stable, we'll have cured their CGD (chronic granulomatous disease). But we don't know. It's very early. The first one, the little boy, is only 70 to 80 days out; the second one, the 24-year-old, is only 40 days out," Harry Malech, deputy chief of the NIAID Laboratory of Host Defenses, said at the end of December.

He spoke of the first two patients with CGD to undergo allogeneic peripheral blood stem cell transplantation under a new protocol that draws upon recent advances in blood stem cell purification and transplantation immunology. A third patient underwent the procedure in mid-January.

Three novel features of this protocol are, first, that the patient receives milder treatments to suppress their own marrow; second, that the stem cells are derived from the donor's blood by apheresis instead of marrow; and third, most of the lymphocytes are removed from the transplanted donor cells to reduce early graft vs. host disease, with supplemental donor lymphocyte transfusions used later to "stabilize" the graft.

The goal is to correct the neutrophil defect that underlies CGD (see box)—and not all the neutrophils have to be in good working order to do that, Malech notes. Correction of only 5 to 10 percent of the body's neutrophils will result in clinical cure, he says. But numbers are only half the battle—"durability" of the correction is also critical.

CGD was recognized as an entity only in the 1960s and, reflective of the capability of the medical community to treat it then, was given the name "fatal CGD of childhood." Thanks to the work of John Gallin, now Clinical Center director, and others, Malech says, "fatal" fell away as an inevitability, and it became possible for many patients to live into adulthood, with frequency and severity of infection reduced by prophylactic antibiotic and interferon gamma regimens.

"But there's a sword of Damocles hanging over patients' heads. They get sudden, overwhelming infections and recurring infections with accumulations of inflammatory cells and scarring that increasingly compromise lung or liver function. Despite improvements, we still have about 1 to 2 percent

yearly mortality. Imagine a roomful of 100 children where one or two will die each year. Would you not consider that terrible?"

Malech's lab focused first on autosomal recessive CGD, which led to the discovery and cloning of the genes underlying the p47^{phox} and p67^{phox}-deficient types of CGD. By 1992, all four CGD-causing genes had been cloned. "I decided to aim my laboratory program toward the development of gene therapy for CGD," Malech says, thanking NHGRI's Michael Blaese for his early assistance, "and I viewed this as a very long-term project."

A clinical trial of gene therapy for CGD in 1995–1996 took the patients' own purified blood stem cells, corrected them with a retrovirus vector outside the body, and returned the cells to the patient. This resulted in several months' worth of endogenous production of "very tiny numbers" (1 in 2,000 to 10,000) of functionally corrected neutrophils. In the current version of this trial, improved methods of stem cell harvest and purification with more efficient gene transfer have resulted in a fourfold increase in peak numbers of corrected cells in the patients. Although the effect decreases with time, "we still see tiny numbers of corrected cells—at this point beyond eight months," Malech says, observing that "while this is exciting scientifically, we have a way to go with gene transfer." He acknowledges that clinical benefit now is unlikely but emphasizes that this proven durability will be crucial in conjunction with strategies to enhance the engraftment of the incoming gene-corrected cells.

"We are learning things about mild regimens of marrow conditioning from our allogeneic transplant program that we may be able to apply to the gene therapy approach," he notes. Currently, the allogeneic transplant approach applies only to patients with a fully matched sibling donor. The development of gene therapy, then, is still an important goal for the other patients, and the autologous stem cell gene transfer and allogeneic peripheral stem cell transplantation programs proceed apace, "intellectually connected." Both approaches rely, for instance, on novel machinery using antibodies and magnetic beads to extract and purify stem cells. Additional processing in the allogeneic transplant protocol uses an antibody developed by NCI's



John Crawford

Harry Malech delivers allogeneic stem cells to the first CGD patient on the new protocol. The donor (a younger sister) and parents look on. Ron Gress to deplete lymphocytes.

A major clinical advance in stem cell biology was the use of recombinant marrow growth factors to cause large numbers of stem cells to come out of the bone marrow and enter the bloodstream, a process called mobilization. This made possible a "revolution" in transplantation, Malech says. "One could use apheresis and special purification methods to separate out large numbers of the desired cells for either autologous or allogeneic transplantation," he says, extending his scientific thanks for their roles in his studies to Susan Leitman and Elizabeth Read, who run the apheresis and special processing units, respectively, in the transfusion medicine department.

As recently as five years ago, he marvels, "the concept of using peripheral blood-mobilized stem cells instead of bone marrow as a source for transplantation was considered revolutionary; now it's almost become the standard of care."

Recovering stem cells from the blood rather than the marrow is easier on the donor (for allogeneic transplants) or the patient (for autologous transplants) and lends itself to repeat and more exact procedures. "The jury is still out" on whether peripheral blood stem cells are "as fit" as marrow cells to do the job, but it "appears they are," Malech says.

The new allogeneic transplantation protocol was crafted by principal investigator Mitchell Horwitz, a NIAID clinical associate who was formerly with NHLBI and conceived of a collaboration between the CGD team and NHLBI's John Barrett. "A unique opportunity for our CGD patients occurred because of John Barrett's novel work in the NHLBI transplant program for cancer patients," Malech relates. "He has been piloting the use of mild conditioning regimens, relying in part on the immune system of the incoming donor cells—the lymphocytes—to act as a wedge to enhance engraftment of donor progenitor cells in recipient marrow."

The investigators hope to demonstrate in the CGD allogeneic transplant study that it is possible to achieve a cure with permanent donor cell engraftment while reducing or eliminating the dangerous and potentially fatal side effects of transplantation. The ability to ward off graft vs. host disease and to use milder ablative therapy to effect a transplant that results in a "stable coexistence of both donor and recipient cells, hopefully for a lifetime," Malech says, could also apply to the treatment of many other inherited diseases of blood cells. ■

CGD at a Glance

Chronic granulomatous disease (CGD) is a group of inherited disorders of neutrophil dysfunction leading to recurrent bacterial and fungal infections. The neutrophil fails to produce superoxide and, consequently, hydrogen peroxide, a crucial host defense against daily infection. Genetically, CGD is four different diseases—based on the absence of any one of four subunits of the phagocytose NADPH oxidase enzyme—though phenotypically it's one disease with varying severity.

About 25,000 people are affected worldwide at any given time. Two thirds have an X-linked form of the disease; they lack one particular protein—gp91^{phox} ("phox" stands for "phagocytose oxidase")—normally encoded by a gene on the X chromosome. Most of the rest have an autosomal recessive form due to the absence of p47^{phox}, usually carried on chromosome 7; the other two forms occur in the remaining 2 to 3 percent of the affected population and arise from the absence of either p22^{phox} or p67^{phox}, encoded on chromosomes 16 and 1, respectively. ■

ALTERNATIVES: JONAS MOVES ON
continued from page 1

The previous director had resigned in frustration, and there was tension among OAM, its advisory committee, involved congressional parties, and others.

Jonas was here for three-and-a-half years on a detail from the Army. By most accounts, he stabilized OAM operations and solidified both its place in the spectrum of NIH research and its mandate to apply scientific method and evaluation to alternative medical practices—and let the public know the state of the art.

During his watch, collaborative projects with NIH research institutes have been established, centers around the country have been funded to do complementary and alternative medicine research, and representatives of the alternative and mainstream scientific communities constructed a strategic plan for OAM activities, released last August. Two months later, Congress elevated the OAM to Center status—the National Center for Complementary and Alternative Medicine (NCCAM)—with an annual budget of \$50 million (from \$20 million the previous fiscal year); and the *Journal of the American Medical Association* and the nine AMA Archives Journals published coordinated “theme” issues with more than 80 articles and editorials on alternative medicine. The *JAMA* issue included an editorial by Jonas.

Jonas is returning to a faculty position at the Uniformed Services University of the Health Sciences in Bethesda, Maryland, where 40 percent of his time will be spent doing research and the rest will be divided between his family practice and teaching.

His NIH successor, Jonas believes, should be a practicing physician with a sense of the public’s perspective or, if not a physician, someone who “listens very closely to that perspective.” To focus the science in relevant areas, he says, “you have to both hear what the public is asking and examine where the data are leading.” Jonas was interviewed by *The NIH Catalyst* in December, several weeks before his departure.

Q: What do the establishment of NCCAM and the appearance of the alternative medicine edition of *JAMA* and its affiliated journals indicate about the progress of alternative medicine?

Jonas: They reflect the increasing maturity of the field. As I said in my *JAMA* editorial, complementary and alternative medicine (CAM) has come of age in the scientific community—it’s been “of age” as far as the public is concerned for a long time, and now the mainstream community is beginning to see its importance.

Historically, this is not the first time unconventional practices have become popular. Typically, the orthodox field fights these practices for a while, then starts to examine them, and gradually adopts certain ones. Any time new ideas are brought into established areas, both sides risk changing, and both the new ideas and the old change—hopefully. Both sides should change, of course, because nobody has the corner on truth, not statesmen or scientists.

The establishment of NCCAM at NIH indicates that the capacity to do research and the interest among researchers have grown. In addition, alternative practitioner groups are starting to express an interest in science. Both sides, hopefully, are coming to focus on science, and the Center at NIH reflects that social phenomenon.

Q: Do you think congressional pressure was necessary?

Jonas: Any established group, whether in medicine, science, or politics, generally doesn’t like change, so there’s usually some element of coercion at some point. But once people within the orthodox community begin to see where there could be value, they move toward it themselves. In the last three-and-a-half years, I’ve seen a tremendous increase in interest from the mainstream community. When I started here, most people who approached me were practitioners in the CAM field who wanted a particular practice sanctioned. Now the vast majority who contact me are mainstream scientific groups who want to know how to get a grant in these areas, or what topics are of most interest, or how best they can pursue a specific research idea they have. This is progress.



Fran Pollner

Wayne Jonas

Q: What do you think engendered this interest—the public or the science?

Jonas: I think it’s a combination of things. The public may have brought the attention of scientists to alternative medicine, but that by itself is not sufficient to move scientists into an area of research unless they can see testable hypotheses and the possibility of useful results. And, of course, there’s more money available now.

Q: Which do you think are some of the testable hypotheses?

Jonas: NCCAM is involved in testing some of these right now: looking at the clinical safety and efficacy of herbal remedies; exploring the mechanisms of acupuncture analgesia; and testing the hypotheses and practices of chiropractic, which is something chiropractors themselves have gravitated toward.

As an “office,” OAM did not have the authority or capacity to fund research directly. It used its funds to supplement or to co-fund projects based in other NIH institutes or to develop new initiatives with the institutes that they would then carry out. I suspect that the bulk of the new Center’s projects will continue to be collaborative, even though Center status confers the capacity to execute and fund its own research. After all, \$50 million will not go that far, and you wouldn’t want to set up a separate infrastructure when the expertise and infrastructure required to carry out good (CAM) research already exist at the NIH. We’re working very closely with NCI, for example, to help identify what look like viable projects, and we supply some of the resources, but NCI uses its existing research structures—cancer research centers and regional oncology groups—to develop and test particular practices and projects.

There are other ways we collaborate with the institutes. We worked with NIAMS to put language on CAM-related research into their fibromyalgia RFA—since that’s an area in which CAM is used extensively—and about 10 percent of the applications that came in were in CAM areas. Should there be outstanding applications in those areas that NIAMS supports, we’ll back them up with some resources. We’ve done similar things with

NHLBI, which is currently soliciting to re-fund their SCORS—their centers for cardiovascular disease research.

Last year, we cosponsored with 12 of the institutes a consensus development conference on acupuncture, an area ripe for both basic and clinical research. Following the conference, we had a series of meetings with the institutes to develop RFAs, and we released an RFA last year for examining acupuncture's effects on pain, stroke, asthma, and neurological and immunological conditions. There's also a trans-agency CAM committee that Dr. Varmus set up last December (1997) that includes people from the institutes and from other agencies, like the Food and Drug Administration and the Centers for Disease Control and Prevention.

Q: With which institutes have you been most active?

Jonas: We've worked with almost all the institutes through one or another mechanism and have developed initiatives, new projects, with about half of them. We've worked very closely with NIMH, NIAMS, NICHD, NCI, NHLBI, NIDCR, NIDA, NCRR, NINR, NIAAA, and others. We have an intramural research training program, a research support mechanism whereby intramural labs put together applications for CAM-related projects and also provide some postdoctoral research training in these areas. A board of intramural scientists reviews those applications and makes recommendations to us. Then those institutes execute those projects. For example, NIAAA was interested in examining more objective markers of the neurophysiological effects of acupuncture in alcoholics. They recruited [an intramural] fellow to set up a project using functional MRI [magnetic resonance imaging] and PET [positron-emission tomography] scanning.

Q: How many intramural projects are there?

Jonas: There are four funded now. In addition to the NIAAA acupuncture project, there's an examination of transcranial electrical stimulation and its effect on learning (NINDS); an examination of the anticancer effects of herbal folk remedies (NCI); and a series of studies on the impact of changing expectations on the clinical analgesic effects and neurophysiologic correlates of acupuncture analgesia and placebo (NIDCR).

Q: What attracted you to the OAM director position?

Jonas: Before coming here, I ran a postdoctoral research training program at the Walter Reed Army Institute of Research [in Washington]. Prior to that, I had done health promotion policy at the Army Surgeon General's office and served on the staff of a family practice residency program in Fort Belvoir, Virginia. I got interested in CAM when I was a medical officer stationed in Germany and running a family practice clinic in the early 1980s. I speak a fair amount of German and went out to the local German medical societies to find out what was going on. What I found was that they were incorporating unconventional practices, such as acupuncture, herbs, and homeopathy, into their medical practices. This got me intrigued, and I began to study some of these selectively.

I came here, first of all, because I love science and I'm very curious. My main goal was to get the office operating in a way that it could do high-quality research and be integrated into the operations of the NIH. I wanted it to grow roots into the NIH and develop collaborative relationships—which has happened. We have 50 projects up and running and 13 centers.

We've also supported critical evaluation of existing CAM research: We worked with the Cochrane Collaboration, which is a group that systematically reviews randomized controlled trials in all health-care areas. We have a clearinghouse that provides the public with information on OAM activities and research. We've worked with NLM to review over 600 CAM-related publications and journals. We've pulled together a CAM citation index from major data sources and provided it on our home page (with over 100,000 citations), so the public can search it.

Q: What do you see as NIH's proper role in exploring or defining alternative therapeutic approaches?

Jonas: I think NIH should provide the benchmark of quality science, the gold standard for doing research in these areas. It should also do basic and other research in CAM areas that are not likely to be funded through the private sector for lack of financial incentives. There's a strategic plan for OAM, developed

over the last three years, that was released last August and outlines very clearly what the complementary and mainstream communities have agreed on are good directions for the office to go. Two months after its release, though, the Office was dissolved and the Center was created, so we'll see what happens.

Q: What did you most enjoy during your time here? What did you find unpleasant or frustrating?

Jonas: The most exciting thing for me is working with scientists who suddenly see something important that can be tested, an idea that suddenly crystallizes. One time, we were working with six different institutes and the Office of Behavioral and Social Sciences Research to examine the whole area of religion and spirituality. A scientist from NIAID was looking through background material when he suddenly looked up with a surprised expression and said, 'It looks like some of these religious practices may have effects on the immune system.' Something had triggered a new perception, a way to study the neurobiology, if you will, of religion and religious practices.

And on the difficult side, as Daniel Boorstin said, and I quoted him in the *JAMA* editorial: The greatest obstacle to discovery is the illusion of knowledge—not difficulties in getting knowledge or even ignorance. This includes practitioners who don't feel the need to test their claims—or even claim that they can't be tested—and scientists who dismiss the idea of testing what they can't explain, an unusual mysterious phenomenon they can't explain. Both are arrogance, and both are obstacles to good research.

Q: There's a quality to the poems you submitted to the *Catalyst* [last year, a bit too late to be included in the May-June 1998 issue with other offerings from hidden NIH poets] that seems to express some of what you are describing, especially one called "Enlightenment in Fog."

Jonas: I was on a camping trip with my daughter in the mountains of West Virginia, looking to the east, and saw as the sun was coming up these mountains kind of emerge from the mist. I got one of those serene feelings you get in the mountains, and that poem came to me.

You could think of CAM in terms of a

PEOPLE

RECENTLY TENURED

hazy area that we attribute to some kind of mystical thing that through good research and a little light (wisdom) gradually emerges as a normal process—something we can explain, investigate, and control. Back in the Middle Ages when Europe was being devastated by bubonic plague epidemics, the prominent theory was that it was God's wrath and it would be playing God to investigate it, try to interfere with the process, and reduce the death rate. We get the same attitudes today if we start to investigate so-called "mystical" or unexplained observations. As scientists, I think our attitude should be that maybe these are just normal processes that with good research we can understand and control. Surprisingly, this idea is threatening. Most people want to stick to their beliefs above all else, and good science threatens that. So, yes, "enlightenment in fog"—helping something emerge from a fog of unclear ideas by throwing the light of science on it—this is what investigating complementary and alternative medicine is all about. ■

Enlightenment in Fog

Standing on the east side of the bald;
Waiting for the mountains to emerge
from fog;
Perhaps as we grow older
Spiritual signs grow more subtle,
Until they are indistinguishable
From normal life.

—Wayne B. Jonas
4 Sept. 1997

Small Talk Rock

No words can capture
the color of soft morning light
in that early time
when it illuminates
but does not strike.

No discussion can release
the deep desire I see you
have forced against the bars
of this small talk cage we make
and through which it peeks out.

There is a place I go
during times of great despair or joy
that is like a warm rock
in the sun;
and there you are.

—Wayne B. Jonas
19 April 1997

Ding J. Jin received his Ph.D. from the University of Wisconsin-Madison in 1988 and did postdoctoral work there until joining the NCI Laboratory of Molecular Biology in 1991. He is currently a senior investigator.

The goal of my research program is to understand the transcription machinery and its mechanism using *Escherichia coli* as a model system. Regulation of transcription is a key step in controlling gene expression in all cells. The basic structure and function of RNA polymerase (RNAP)/RNAP-associated proteins are conserved throughout evolution.

The sophisticated genetics and advanced biochemistry of the *E. coli* system facilitate the analysis of structure-function relationships of RNAP and the elucidation of transcription mechanisms at the molecular level. *E. coli* RNAP exists in two forms: core ($\alpha_2\beta\beta'$) and holoenzyme ($\alpha_2\beta\beta'\sigma$). While core RNAP is capable of transcription elongation and termination, initiation requires a sigma-containing holoenzyme. There are multiple sigma factors in *E. coli*, and each holoenzyme specifically recognizes a set of genes (a regulon).

Thus, the binding of core RNAP with sigma factors to form different holoenzymes is, operationally, the first step in transcription initiation, and a critical step in controlling global gene expression. An ongoing project in my laboratory is to investigate the interplay between core RNAP and sigma factor(s), with an emphasis on the role of core RNAP. We have developed genetic systems to identify the sites in core RNAP that bind to sigma factors and the elements that influence the interaction between core RNAP and sigma factors.

We have identified other site(s) in RNAP that are important for RNAP functions. For example, we showed that the antibiotic rifampicin-binding sites in RNAP are involved in transcription initiation, in addition to elongation and termination as previously described, indicating that they are at or near the catalytic center of RNAP.

We found that β and β' RNAP mutants altered interaction with promoters, demonstrating that transcription initiation is a concerted action of sigma

factor(s) and core RNAP.

Recently, we identified a novel RNAP-associated protein, RapA. RapA, a bacterial homolog of SWI2/SNF2 family, is an ATPase. We showed that RapA forms a stable complex with RNAP and that binding to RNAP stimulates its ATPase activity, thus demonstrating that the two proteins interact physically as well as functionally. Currently, we are studying the regulation of the *rapA* gene and the function of RapA inside the cell.

Promoter clearance is a transition step between transcription initiation and elongation, during which RNAP also synthesizes nonproductive initiation products at many promoters.

By studying the mutant RNAPs that altered productive and nonproductive initiation, I illustrated that promoter clearance is a rate-limiting step for gene expression at some promoters. Also, I demonstrated that the rate of incorporation of initially transcribed nucleotide(s) at a critical position in nascent RNA determines the switch between nonproductive and productive syntheses during promoter clearance, indicating a kinetic mechanism analogous to the regulation of elongation and termination-antitermination.

Recently we have focused on the mechanism of the stringent (nutrient starvation) response, an important but poorly understood biological process. By analysis of the mutant RNAPs that exhibited a nutrient starvation response phenotype even in rich media, we demonstrated that modulation of the stability of open complexes between RNAP and stringent promoters is a regulatory step.

We proposed a new model to link transcription and the stability of the initiation complexes at this class of promoters, and to account for differential distribution of RNAP molecules to different sets of genes in response to environmental cues (nutrient richness or starvation) in the cell.

Our hypothesis thus provides a basis for further experiments to determine the *cis* and *trans* elements important for co-ordinated regulation of the nutrient starvation response.



Fran Pollner
Ding Jin

Minoru S. H. Ko received his M.D. degree in 1986 and his Ph.D. in 1991 from Keio University School of Medicine in Tokyo. He was a tenured associate professor at the Center for Molecular Medicine & Genetics at Wayne State University in Detroit until 1998, when he arrived at NIA, where he is now head of the Developmental Genomics and Aging Section, Laboratory of Genetics.

My research interest is in the mechanisms of cell differentiation in early mammalian development, in terms of global gene regulatory networks and cascades. In one earlier study, using a steroid hormone inducible gene, I demonstrated a stochastic component in the regulation of expression of individual genes at a single cell level. I have also developed three methods that aid in profiling systematic gene expression in specific cell types. These are: 1) PCR-based amplification of a complex mixture of cDNAs, which allows the analyses of a cohort of genes expressed in the small number of cells; 2) a way to construct a normalized cDNA library in which the abundance of individual cDNA species is equalized; and 3) an efficient PCR-based method for localizing mouse cDNAs or expressed sequence tags (ESTs) on the genetic map.

These methods, combined with high-throughput DNA sequencing technology, have allowed my group to generate many developmental and tissue-specific cDNA libraries, including more than 30,000 ESTs, with 1,000 new genes placed on the mouse genetic map, over the last 5 years. The cDNA clones and ESTs are derived from preimplantation and peri-implantation mouse embryos. We are using the ESTs both for expression profiling of special cell types and for map-driven gene discovery. In further steps to understand gene regulatory networks, we use selected cDNAs as probes for *in situ* hybridization to mouse embryonic and fetal preparations, and we organize microarrays of sets of the cDNA clones for systematic analysis of coexpression patterns.

As a model system, we have been using extraembryonic tissue development. The first differentiation event in



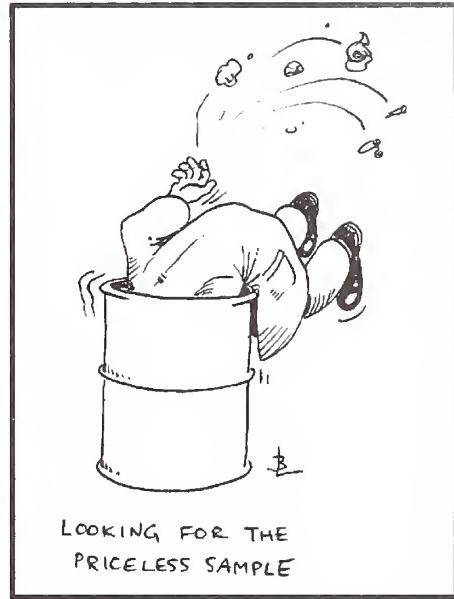
Jerri Muller

Minoru Ko

mammalian embryos generates two distinct lineages: the trophectoderm (TE) and the inner cell mass (ICM). The ICM will eventually become most of the embryo proper, while the TE will eventually become the extraembryonic tissues such as placenta. While analyzing a cohort of genes expressed in the ectoplacental cone, a derivative of the TE, from the 7.5-day postconception (dpc) mouse embryo, we have found that notable subsets of genes are clustered in subregions of the mouse genome. Most prominent is the t-complex, which has been a focus of research for a half century because of unique features including the presence of many embryonic lethal mutant loci and large inversions of the genomic regions. We speculate that

clustering is associated with both coexpression and monoallelic expression of genes. We are currently sequencing the genome segment of mouse t-complex.

One aspect of extraembryonic tissue development is directly relevant to a classic problem in aging research: the difference between "mortal" and "immortal," or pluripotent, cells. The ICM cells of mouse embryos at 3.5 dpc can indeed grow indefinitely in culture, whereas the outer layer (TE) cells are already limited in lifespan. We are applying the gene-profiling methods and gene cohorts we have developed to compare gene expression in the two types of cells in the hope of identifying genes that turn on or off to initiate "mortality." ■



LOOKING FOR THE PRICELESS SAMPLE



THE EVER POPULAR "LAB-COAT-CAUGHT-IN-THE-DOORNOOS" ARABESQUE.

Neurobiology Interest Group

The Neurobiology Interest Group now meets Fridays, twice a month, from 4:30 to 6:30 at the Cloister's rathskellar. Typically, the formal portion of the meeting will be followed by a social hour with refreshments.

The purpose of the group is to promote interactions between NIH laboratories pursuing diverse approaches to the study of the nervous system. The format—an introductory overview by the section or lab PI, followed by a presentation by a postdoctoral fellow—is meant to encourage lab-meeting-style discussions and collaborations among fellows.

Co-chairs (and contact persons) are Chip Gerfen, at 496-4341 or <gerfen@helix.nih.gov>, and Chris McBain, at 402-4778 or <chrismcb@codon.nih.gov>. Anyone interested in learning more about the interest group may visit its website at <<http://intra.ninds.nih.gov/nig/>> and subscribe to its mailing list. ■

CALL FOR CATALYTIC REACTIONS

In this issue, we are asking for your reactions in four areas: clinical research morale, Centers of Excellence, complementary and alternative medicine, and an NIH graduate program.

Send your responses on these topics or your comments on other intramural research concerns to us via e-mail:
<catalyst@nih.gov>; fax: 402-4303; or mail: Building 1, Room 209.

In Future Issues...

- The NIH Academy
- Mentoring Survey
- Malaria Research At the Clinical Center

- 1) Some clinical research leaders see signs of rising spirits among clinical investigators. Do you agree? What additional steps should be taken to rejuvenate clinical research at NIH?
- 2) What is your reaction to the "Centers of Excellence" concept (see page 1)? In what research areas do you think NIH could most benefit from establishing such centers?
- 3) Complementary and alternative medicine has taken several years to settle in and get rolling at NIH (see page 1), and a National Center of Complementary and Alternative Medicine has now been established here. What advice would you give to a new NCCAM director?
- 4) Following emerging recommendations of the Slavkin committee, NIH will explore the possibility of establishing a graduate program in clinical research and an Academy to train a more diverse cadre of biomedical investigators. *The Catalyst* plans to focus on these possibilities in the next issue. Is the time right for these changes? What steps does NIH need to take to prepare itself for additional mentoring and teaching activities?

The NIH Catalyst is published bi-monthly for and by the intramural scientists at NIH. Address correspondence to Building 1, Room 209, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; fax: (301) 402-4303; e-mail: <catalyst@nih.gov>

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